

Complete Summary

GUIDELINE TITLE

Obstetrical complications associated with abnormal maternal serum markers analytes.

BIBLIOGRAPHIC SOURCE(S)

Gagnon A, Wilson RD, Audibert F, Allen VM, Blight C, Brock JA, Desilets VA, Johnson JA, Langlois S, Summers A, Wyatt P. Obstetrical complications associated with abnormal maternal serum markers analytes. J Obstet Gynaecol Can 2008 Oct;30(10):918-32. [162 references] [PubMed](#)

GUIDELINE STATUS

This is the current release of the guideline.

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SCOPE

DISEASE/CONDITION(S)

Obstetrical complications associated with abnormal levels of maternal serum markers analytes, including fetuses at risk of:

- Open neural tube defects
- Chromosomal abnormalities (aneuploidy), in particular trisomy 21 and trisomy 18

GUIDELINE CATEGORY

Counseling
Prevention

Risk Assessment
Screening

CLINICAL SPECIALTY

Hematology
Medical Genetics
Obstetrics and Gynecology
Pediatrics

INTENDED USERS

Advanced Practice Nurses
Physician Assistants
Physicians

GUIDELINE OBJECTIVE(S)

- To provide a summary of the obstetrical risks associated with values outside the normal range for the five common first and second trimester serum screening markers: alphafetoprotein, human chorionic gonadotropin, unconjugated estriol, inhibin-A, and pregnancy associated plasma protein-A
- To review the obstetrical outcomes associated with abnormally elevated or decreased level of one or more of the most frequently measured maternal serum marker analytes used in screening for aneuploidy
- To provide guidance to facilitate the management of pregnancies that have abnormal levels of one of more markers and to assess the usefulness of these markers as a screening test

TARGET POPULATION

Pregnant women in the first or second trimester

INTERVENTIONS AND PRACTICES CONSIDERED

Screening/Risk Assessment

1. Laboratory screening
 - Maternal serum alpha-fetoprotein (AFP)
 - Free or total beta-human chorionic gonadotropin (hCG)
 - Unconjugated estriol
 - Inhibin A
 - Pregnancy-associated plasma protein A (PAPP-A)
2. Genetic counseling
3. Imaging
 - Ultrasound, including uterine artery Doppler measurement
 - Magnetic resonance imaging (MRI)
4. Fetal surveillance plan with patient education

MAJOR OUTCOMES CONSIDERED

- Risks and benefits of diagnostic procedures
- Predictive value of ultrasound markers of aneuploidy
- Predictive value of diagnostic tests for detection of fetal chromosomal abnormalities

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

The Cochrane Library and Medline were searched for English-language articles published from 1966 to February 2007, relating to maternal serum markers and perinatal outcomes. Search terms included PAPP-A (pregnancy associated plasma protein A), AFP (alpha-fetoprotein), hCG (human chorionic gonadotropin), estriol, unconjugated estriol, inhibin, inhibin-A, maternal serum screen, triple marker screen, quadruple screen, integrated prenatal screen, first trimester screen, and combined prenatal screen.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Quality of Evidence Assessment*

I: Evidence obtained from at least one properly designed randomized controlled trial.

II-1: Evidence obtained from well-designed controlled trials without randomization.

II-2: Evidence obtained from well-designed cohort (prospective or retrospective) or case-control analytic studies, preferably from more than one center or research group.

II-3: Evidence obtained from comparisons between times or places with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of treatment with penicillin in the 1940s) could also be included in this category

III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

* Adapted from the Evaluation of Evidence criteria described in the Canadian Task Force on Preventive Health Care.

METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

All study types were reviewed. Randomized controlled trials were considered evidence of the highest quality followed by cohort studies. Key individual studies on which the recommendations are based are referenced. Supporting data for each recommendation are summarized with evaluative comments and references.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Not stated

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Classification of Recommendations*

- A. There is good evidence to recommend the clinical preventive action
- B. There is fair evidence to recommend the clinical preventive action
- C. The existing evidence is conflicting and does not allow to make a recommendation for or against use of the clinical preventive action; however, other factors may influence decision-making
- D. There is fair evidence to recommend against the clinical preventive action
- E. There is good evidence to recommend against the clinical preventive action
- L. There is insufficient evidence (in quantity or quality) to make a recommendation; however, other factors may influence decision-making

*Adapted from the Classification of Recommendations criteria described in the Canadian Task Force on Preventive Health Care.

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

This technical update has been reviewed by the Genetics Committee of the Society of Obstetricians and Gynaecologists of Canada (SOGC) and reviewed and approved by the Executive of the SOGC.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

The quality of evidence (I-III) and classification of recommendations (A-E) are defined at the end of the "Major Recommendations."

Maternal Serum Pregnancy Associated Plasma Protein-A

Summary Statement

An unexplained level of a maternal serum marker analyte is defined as an abnormal level after confirmation of gestational age by ultrasound and exclusion of maternal, fetal, or placental causes for the abnormal level. **(III)**

Recommendations

1. In the first trimester, an unexplained low pregnancy associated plasma protein A (PAPP-A) (< 0.4 multiples of the median [MoM]) and/or a low human chorionic gonadotropin (hCG) (< 0.5 MoM) are associated with an increased frequency of adverse obstetrical outcomes, and, at present, no specific protocol for treatment is available. **(II-2A)** In the second trimester, an unexplained elevation of maternal serum alpha-fetoprotein (AFP) (> 2.5 MoM), hCG (> 3.0 MoM), and/or inhibin-A (≥ 2.0 MoM) or a decreased level of maternal serum AFP (< 0.25 MoM) and/or unconjugated estriol (< 0.5 MoM) are associated with an increased frequency of adverse obstetrical outcomes, and, at present, no specific protocol for treatment is available. **(II-2A)**
2. Pregnant woman with an unexplained elevated PAPP-A or hCG in the first trimester and an unexplained low hCG or inhibin-A and an unexplained elevated unconjugated estriol in the second trimester should receive normal antenatal care, as this pattern of analytes is not associated with adverse perinatal outcomes. **(II-2A)**
3. The combination of second or third trimester placenta previa and an unexplained elevated maternal serum AFP should increase the index of suspicion for placenta accreta, increta, or percreta. **(II-2B)** An assessment (ultrasound, Magnetic resonance imaging [MRI]) of the placental-uterine interface should be performed. Abnormal invasion should be strongly

- suspected, and the planning of delivery location and technique should be done accordingly. **(III-C)**
4. A prenatal consultation with the medical genetics department is recommended for low unconjugated estriol levels (<0.3 MoM), as this analyte pattern can be associated with genetic conditions. **(II-2B)**

Combined Assessment of Multiple Markers

Recommendations

5. The clinical management protocol for identification of potential adverse obstetrical outcomes should be guided by one or more abnormal maternal serum marker analyte value rather than the false positive screening results for the trisomy 21 and/or the trisomy 18 screen. **(II-2B)**

Multiple Pregnancies

Summary Statement

Abnormally elevated levels of serum markers are associated with adverse pregnancy outcomes in twin pregnancies, after correction for the number of fetuses. Spontaneous or planned multifetal reductions may result in abnormal elevations of serum markers. **(II-2)**

Factors Affecting the Levels of Various Maternal Serum Markers

Recommendations

6. Pregnant woman who are undergoing renal dialysis or who have had a renal transplant should be offered maternal serum screening, but interpretation of the result is difficult as the level of serum hCG is not reliable. **(II-2A)**

Evaluation and Management of Women with One or More Abnormal Serum Markers

Second Trimester Evaluation

Recommendations

3. (Same recommendation as #3 above) The combination of second or third trimester placenta previa and an unexplained elevated maternal serum AFP should increase the index of suspicion for placenta accreta, increta, or percreta. **(II-2B)** An assessment (ultrasound, magnetic resonance imaging [MRI]) of the placental-uterine interface should be performed. Abnormal invasion should be strongly suspected, and the planning of delivery location and technique should be done accordingly. **(III-C)**
7. Abnormal maternal uterine artery Doppler in association with elevated maternal serum AFP, hCG, or inhibin-A or decreased PAPP-A identifies a group of women at greater risk of intrauterine growth restriction (IUGR) and gestational hypertension with proteinuria. Uterine artery Doppler

measurements may be used in the evaluation of an unexplained abnormal level of either of these markers. **(II-2B)**

Maternal and Fetal Surveillance

Recommendations

8. Further research is recommended to identify the best protocol for pregnancy management and surveillance in women identified at increased risk of adverse pregnancy outcomes based on an abnormality of a maternal serum screening analyte. **(III-A)**
9. In the absence of evidence supporting any specific surveillance protocol, an obstetrician should be consulted in order to establish a fetal surveillance plan specific to the increased obstetrical risks (maternal and fetal) identified. This plan may include enhanced patient education on signs and symptoms of the most common complications, increased frequency of antenatal visits, increased ultrasound (fetal growth, amniotic fluid levels), and fetal surveillance (biophysical profile, arterial and venous Doppler), and cervical length assessment. **(III-A)**

Therapeutic Approaches and Interventions

Recommendations

10. Limited information suggests that, in women with elevated hCG in the second trimester and/or abnormal uterine artery Doppler (at 22–24 weeks), low-dose aspirin (60–81 mg daily) is associated with higher birthweight and lower incidence of gestational hypertension with proteinuria. This therapy may be used in women who are at risk. **(II-2B)**
11. Further studies are recommended in order to assess the benefits of low-dose aspirin, low molecular weight heparin, or other therapeutic options in pregnancies determined to be at increased risk on the basis of an abnormal maternal serum screening analyte. **(III-A)**

Multiple Markers Screen as a Screening Test for Obstetrical Complications

Recommendations

12. Multiple maternal serum markers screening should not be used at present as a population-based screening method for adverse pregnancy outcomes (such as preeclampsia, placental abruption, and stillbirth) outside an established research protocol, as sensitivity is low, false positive rates are high, and no management protocol has been shown to clearly improve outcomes. **(II-2D)**

When maternal serum screening is performed for the usual clinical indication (fetal aneuploidy and/or neural tube defect), abnormal analyte results can be utilized for the identification of pregnancies at risk and to direct their clinical management. **(II-2B)** Further studies are recommended to determine the optimal screening method for poor maternal and/or perinatal outcomes. **(III-A)**

Definitions:

Quality of Evidence Assessment*

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- L. There is insufficient evidence (in quantity or quality) to make a recommendation; however, other factors may influence decision-making

*The quality of evidence reported in these guidelines has been adapted from The Evaluation of Evidence criteria described in the Canadian Task Force on Preventive Health Care.

**Recommendations included in these guidelines have been adapted from the Classification of Recommendations criteria described in the Canadian Task Force on Preventive Health Care.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for each recommendation (see "Major Recommendations").

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

The benefit expected from this guideline is to facilitate early detection of potential adverse pregnancy outcomes when risks are identified at the time of a maternal serum screen. It will help further stratification of risk and provide options for pregnancy management to minimize the impact of pregnancy complications.

POTENTIAL HARMS

The potential harms resulting from such practice are associated with the so called false positive (i.e., uncomplicated pregnancies labelled at increased risk for adverse perinatal outcomes), the potential stress associated with such a label, and the investigations performed for surveillance in this situation.

QUALIFYING STATEMENTS

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This document reflects emerging clinical and scientific advances on the date issued and is subject to change. The information should not be construed as dictating an exclusive course of treatment or procedure to be followed. Local institutions can dictate amendments to these opinions. They should be well documented if modified at the local level. None of these contents may be reproduced in any form without prior written permission of the Society of Obstetricians and Gynaecologists of Canada (SOGC).

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Staying Healthy

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

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ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2008 Oct

GUIDELINE DEVELOPER(S)

Society of Obstetricians and Gynaecologists of Canada - Medical Specialty Society

SOURCE(S) OF FUNDING

Society of Obstetricians and Gynaecologists of Canada

GUIDELINE COMMITTEE

Society of Obstetricians and Gynaecologists of Canada Genetics Committee

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Disclosure statements have been received from all members of the committee.

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the [Society of Obstetricians and Gynaecologists of Canada Web site](#).

Print copies: Available from the Society of Obstetricians and Gynaecologists of Canada, La société des obstétriciens et gynécologues du Canada (SOGC) 780 promenade Echo Drive Ottawa, ON K1S 5R7 (Canada); Phone: 1-800-561-2416

AVAILABILITY OF COMPANION DOCUMENTS

None available

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI Institute on March 2, 2009. The information was verified by the guideline developer on March 13, 2009.

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